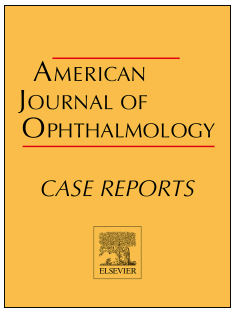


Ritonavir associated maculopathy– multimodal imaging and electrophysiology findings

Roxane Bunod, Alexandra Miere, Olivia Zambrowski, Pierre-Marie Girard, Laure Surgers, Eric H. Souied

PII: S2451-9936(19)30095-7

DOI: https://doi.org/10.1016/j.ajoc.2020.100783

Reference: AJOC 100783

To appear in: *American Journal of Ophthalmology Case Reports*

Received Date: 27 February 2019

Revised Date: 22 March 2020

Accepted Date: 8 June 2020

Please cite this article as: R. Bunod, A. Miere, O. Zambrowski, P.-M. Girard, L. Surgers, E.H. Souied, Ritonavir associated maculopathy– multimodal imaging and electrophysiology findings, *American Journal of Ophthalmology Case Reports* (2020), doi: https://doi.org/10.1016/j.ajoc.2020.100783.

RITONAVIR ASSOCIATED MACULOPATHY– MULTIMODAL IMAGING AND ELECTROPHYSIOLOGY FINDINGS

Short title: Ritonavir associated maculopathy

Roxane Bunod, MD,[1] Alexandra Miere, MD,[1] Olivia Zambrowski, MD,[1] Pierre-Marie Girard, MD, PhD,[2] Laure Surgers, MD, PhD[2], Eric H. Souied, MD, PhD[1]

[1]Department of Ophthalmology, Centre Hospitalier Intercommunal de Creteil University Paris Est Creteil, 40 Avenue de Verdun, 94000 Creteil, France

[2]Department of infectious and tropical diseases, Hôpital Saint Antoine, AP-HP and UMRS_ 1136 , Sorbonne Université, F75013 Paris, France

Corresponding author: Eric Souied

Department of Ophthalmology, Centre Hospitalier Intercommunal de Creteil, 40 Avenue de Verdun, 94000 Creteil, France.

Tel: 33-1-45175222.

Fax: 33-1-45175227

Email: esouied@hotmail.com

Financial or material support for the research and the work: none.

The authors have no proprietary interest in the materials used in this study.

Word count for text: 1538.

Word count for references: 248.

Keywords: maculopathy; HIV; antiretroviral medication; ritonavir; multimodal imaging

Summary statement:

We describe the case of a patient 47 year-old HIV patient presenting with bilateral symmetric macular atrophy. Both multimodal imaging, functional testing of the retina and history of drug exposure are consistent with ritonavir associated maculopathy.

Abstract

Purpose: To report the case 47-year-old patient presenting with severe maculopathy associated with long-term ritonavir treatment.

Methods: Observational case report of one patient and literature review.

Results: A 47 year-old Caucasian man presented with progressive bilateral vision loss for the past 5 years. His medical history included Human Immunodeficiency Virus (HIV) and Hepatitis C Virus (HCV) coinfection since 1992. He was treated by highly active antiretroviral therapy for 24 years including 4 years of didanosine treatment and 18 years of ritonavir treatment. Bilateral extensive macular atrophy with foveal sparing on the left eye and absence of midperipheral/peripheral retina involvement was confirmed on multimodal imaging and functional testing including swept-source OCT angiography and electroretinography.

Conclusion: Ritonavir associated maculopathy is a scarcely described medication-associated retinopathy. In this case, an extensive macular atrophy (with complete loss of photoreceptor, RPE and choriocapillaris layers) and subsequent cone-rod dysfunction appeared after 18 years of ritonavir exposure.

Introduction

Ritonavir is an antiretroviral drug widely used since 1996 for the treatment of human immunodeficiency virus (HIV) infection. It belongs to the class of protease inhibitors that prevent viral replication by blocking the cleavage of viral protein precursors. Because of its inhibition effect on major cytochrome P450 isoforms (CYP3A4, CYP2D6), ritonavir is now used in combination as a pharmaceutic enhancer / booster in highly active antiretroviral therapy. The major side effects are hepatotoxicity, digestive functional disturbances, lipohypertrophy syndrome and the risk of drug interactions due to cytochrome inhibition. Rare cases of retinopathy have been reported in literature since 2011 with heterogeneous phenotypes ranging from macular atrophy, intra retinal cysts, macular telangiectasia[1] to retinitis pigmentosa-like presentation[2]. We report a case of severe maculopathy, defined by structural and functional outer retinal and choriocapillaris disturbances, in an HIV infected patient with18 years ritonavir exposition.

Case Report

A 47-year-old Caucasian male, with a medical history of HIV and Hepatitis C virus (HCV) infection, presented in the Creteil University Eye Hospital complaining of long standing bilateral loss of vision. He reported a progressive visual loss starting 5 years before. He was diagnosed with HIV and HCV in 1992 following abnormal liver function tests and received antiretroviral therapy since 1994.

Table 1 summarizes the antiretroviral treatment taken by the patient since 1994. During this period, the patient was exposed to didanosine for 4 years and to ritonavir for 18 years. The patient had switched to dolutegravir plus etravirine treatment two months before the first ophthalmologic examination.

Last CD4+ count was 425/mm^3 and HIV plasma viral load was undetectable (below 20

copies/ml). Liver aspartate transaminase (AST) and alanine transaminase (ALT) were normal at last follow up. The patient neither had family history of ocular disease nor other medical condition. Neither did he have a history of deafness, renal dysfunction or diabetes. Testing for tuberculosis and syphilis were negative. The patient had no history of HIV retinopathy or Cytomegalovirus (CMV) retinitis.

The patient has never received Pentosan Polysulfate Sodium (PPS) treatment but reported the use of various recreational psychoactive drugs. Namely, he took gamma hydroxybutyrate (GHB) every week from 2009 to 2012, and then inhaled cocaine on a monthly basis from 2012 to 2014. In 2010 he started to take intravenously 4-methyethylcathinone (4-MEC) (Slam practices) several times per month and increased the rate of injections to three times weekly from 2012 to 2014 before reducing injections to once monthly until 2016 when he stopped completely.

On examination, his best corrected visual acuity (BCVA) was 20/50 on the right eye and 20/25 on the left eye. The anterior segment examination on both eyes was unremarkable, with no signs of inflammation. Fundus examination revealed, on both eyes, an extensive area of macular atrophy; the optic nerve, retinal vessels, vitreous and retinal mid- and extreme-periphery were normal without vitreous cells or evidence of prior uveitis or retinitis (figure 1). Infrared reflectance imaging (IR) demonstrated well demarcated, polylobulated hyperreflective macular atrophy converging with peripapillary atrophy. Multiple hyperreflective dots were noted on IR images within the atrophic lesions. On fundus blue laser autofluorescence (FAF), symmetric hypoautofluorescent extensive areas of retinal pigment epithelium (RPE) atrophy were noted, surrounded by a circumferential ring of speckled hyperautofluorescence pattern reaching the temporal arcades (figure 2).

Spectral domain optical coherence tomography (SD-OCT, Spectralis, Heidelberg Engineering, Heidelberg, Germany) revealed complete RPE and outer retinal atrophy

(cRORA) [3] accompanied by outer retinal tubulations (ORT). On the left eye, foveal sparing was noted, with the preservation of the ellipsoid zone. Enhanced depth imaging SD-OCT coupled with IR allowed the colocalization of the hyperreflective dots in IR with choroidal angular hyporeflective cavities, suggestive for choroidal caverns[4] (figure 3). A window defect, characterized by well demarcated hyperfluorescent areas corresponding to outer retinal and RPE atrophy were observed on fluorescein angiography (FA). A heterogeneous hyperfluorescent speckled pattern surrounding the atrophic areas overlapped with the hyperautofluorescent speckle pattern seen on FAF (figure 2). Indocyanine green angiography showed macular hypofluorescent lesions, corresponding to the atrophic areas, with visualization of large choroidal vessels. Widefield swept-source optical coherence tomography angiography (SS-OCTA, PlexElite, Zeiss, Dublin, CA) revealed a large macular area of choriocapillaris alterations on both eyes (figure 4). The 6x6 mm SS-OCTA showed a well demarcated area of choriocapillaris alteration, revealed by the lack of decorrelation signal, allowing visualization of large choroidal vessels.

Besides structural exams, the patient underwent a series of functional tests, including color vision, Goldman and Humphrey visual fields and electrophysiology exams (ffERG and mfERG). Full-field ERG (Moncolor system, Metrovision, Perenchies, France) and multifocal ERG (mfERG, Espion Diagnosys LLC, Lowell, MA) were recorded accordingly to 2015 ISCEV standards with DTL electrodes in mydriasis. Reduced color discrimination in the tritan axis was found on Roth 28-Hue Test. Both Goldman and Humphrey visual fields demonstrated a bilateral central scotoma (figure 5). However, on the left eye, an isle of preserved retinal sensitivity was noted in the foveal area, corresponding to the preserved ellipsoid zone observed on structural SD-OCT. The full field electroretinogram (ffERG) demonstrated a moderated cone-rod dysfunction, associated with an increased flicker delay. Furthermore, multifocal ERG (mfERG) responses are non-discernible from the background

noise with a complete loss of foveal peak. Predominantly on his left eye, non-systematized focal responses are observed corresponding to the preserved ellipsoid zone area seen on SD-OCT. Electrophysiological findings, with retinal dysfunction, were consistent with the structural disturbances seen in this patient (Supplementary material).

Discussion

We report here the case of an HIV positive patient with a long standing loss of vision secondary to bilateral macular atrophy. While HIV retinopathy, opportunistic infections and unusual malignancy are the main causes of retinal complications, drug toxicity has to be considered as a potential cause. Indeed, HIV patients tend to be exposed to multiple medications such as clofazamine, zidovudine, didanosine or ritonavir for which associated retinopathies have been reported.

The patient was exposed to didanosine for 4 years, ritonavir for 18 years but also to 4-methylethylcathinone (4-MEC) for 6 years. 4-MEC are synthetic cathinones that have recently emerged and became a popular recreational drug[5]. A spectrum of adverse effects has been reported by consumers but, to the best of our knowledge, no retinal toxicity has yet been described. Conversely, several case reports have described didanosine retinal toxicity in HIV positive patients[6]. Even though didanosine toxicity generates chorioretinal atrophy and degeneration, it classically involves the retinal midpheriphery. In the present case, the lack of midperipheral choriocapillaris loss was not consistent with didanosine toxicity (figure 4).

The first case series reporting retinal abnormalities in HIV positive patients treated by ritonavir was published in 2011 by Roe et al and described three patients exhibiting various degrees of bilateral macular RPE atrophy, accompanied by macular telangiectasia, cystic spaces and parafoveal intraretinal crystals[1]. It is interesting to note that these three patients had a history of liver dysfunction, as is the case with our patient which had HIV and HCV

coinfection. As studies in humans have demonstrated that ritonavir is primarily eliminated by the hepatobiliary system, it is possible that the liver dysfunction in these patients may have reduced ritonavir elimination and caused increased circulating drug levels. Among the three patients, a large area of complete outer retina and RPE atrophy with foveal sparing comparable to our patient has been observed in the patient having had the longer exposure to ritonavir (5 years). Biancardi et al. reported another case of macular patchy RPE atrophy surrounded, on FAF, by a speckle autofluorescent pattern, similar to our patient[7]. Electrophysiological features of ritonavir associated maculopathy described in a patient having received ritonavir for seven years also demonstrated a slightly reduced ffERG for both eyes and bilateral maculopathy on mfERG[8]. These functional findings are comparable with the electrophysiology exams of our patient.

There were no clinical argument for hereditary maculopathies such as Maternally Inherited Diabetes and Deafness (MIDD), Mitochondrial Encephalomyopathy with Lactic Acidosis and Stroke-like episodes (MELAS), Stargardt disease, Cone-Rod dystrophy, Pattern dystrophy or Central Areolar Choroidal Dystrophy (CACD). However, a limit of our study is the absence of genetic testing for hereditary maculopathies.

Ritonavir toxicity has been studied in animal model[9]. With treatment duration up to 6 months, the main target organs were the liver and the eyes. The corollary of these animal models was the assumption that retinal degeneration and/or retinal pigment epithelium hypertrophy were related to phospholipidosis. Amorphous granular inclusion bodies, characteristic of phospholipidosis, were found on electron micrographs in the retina of mice, rats and dogs. This phenomenon may be in relation with the enzymatic regulation of cholesterol and lipogenic pathways by ritonavir. It has been suggested that intra retinal crystals correspond to phospholipidosis phenomenon[8]. There were no crystal deposits on our patient imaging but this finding seems to be inconstant throughout ritonavir associated

retinopathy in literature, notably absent in cases with extensive atrophy. Another hypothesis regarding ritonavir toxicity is related to the anti-angiogenic effect of ritonavir demonstrated in vitro RPE cell-lines[10]. Given that, vascular endothelial growth factor, a known neurotrophic agent, inhibition by ritonavir may explain RPE degeneration.

In conclusion, although ritonavir associated maculopathy is very uncommon, literature suggests that the natural history of this maculopathy consists of early stage crystalline deposits, RPE degeneration, degenerative cystic spaced and, finally, extensive atrophy, such as our patient. However, further studies are necessary in order to prove a mechanism of toxicity.

References

1. Roe RH, Jumper JM, Gualino V, et al. Retinal pigment epitheliopathy, macular telangiectasis, and intraretinal crystal deposits in HIV-positive patients receiving ritonavir. *Retina (Philadelphia, Pa)*. 2011;31(3):559-565. doi:10.1097/IAE.0b013e3181f0d2c4

2. Papavasileiou E, Younis S, Zygoura V, Quijano C, Jackson TL. RITONAVIR-ASSOCIATED TOXICITY MIMICKING RETINITIS PIGMENTOSA IN AN HIV-INFECTED PATIENT ON HIGHLY ACTIVE ANTIRETROVIRAL THERAPY. *Retin Cases Brief Rep*. 2017;11(4):306-309. doi:10.1097/ICB.0000000000000350

3. Holz FG, Sadda SR, Staurenghi G, et al. Imaging Protocols in Clinical Studies in Advanced Age-Related Macular Degeneration: Recommendations from Classification of Atrophy Consensus Meetings. *Ophthalmology*. 2017;124(4):464-478. doi:10.1016/j.ophtha.2016.12.002

4. Querques G, Costanzo E, Miere A, Capuano V, Souied EH. Choroidal Caverns: A Novel Optical Coherence Tomography Finding in Geographic Atrophy. *Investigative Opthalmology & Visual Science*. 2016;57(6):2578. doi:10.1167/iovs.16-19083

5. Smith PR, Cole R, Hamilton S, West K, Morley SR, Maskell PD. Reporting Two Fatalities Associated with the Use of 4-Methylethcathinone (4-MEC) and a Review of the Literature. *J Anal Toxicol*. 2016;40(7):553-560. doi:10.1093/jat/bkw061

6. Haug SJ, Wong RW, Day S, et al. DIDANOSINE RETINAL TOXICITY. *Retina (Philadelphia, Pa)*. 2016;36 Suppl 1:S159-S167. doi:10.1097/IAE.0000000000001267

7. Biancardi AL, Curi ALL. Retinal Toxicity Related to Long-term Use of Ritonavir. *Retina (Philadelphia, Pa)*. 2016;36(1):229-231. doi:10.1097/IAE.0000000000000695

8. Faure C, Paques M, Audo I. Electrophysiological features and multimodal imaging in ritonavir-related maculopathy. *Documenta Ophthalmologica*. 2017;135(3):241-248. doi:10.1007/s10633-017-9612-z

9. European Medicines Agency. Scientific discussion for the approval of Norvir. http://www.ema.europa.eu/docs/en_GB/ document_library/EPAR_Scientific_Discussion/human/000127/ WC500028725.pdf.

10. Vadlapatla RK, Vadlapudi AD, Pal D, Mukherji M, Mitra AK. Ritonavir inhibits HIF-1α-mediated VEGF expression in retinal pigment epithelial cells in vitro. *Eye (Lond)*. 2014;28(1):93-101. doi:10.1038/eye.2013.240

Table 1. Antiretroviral treatment since 1994

Start of the treatment	End of the treatement	Treatment duration (months)	Antiretroviral treatment
10/8/1994	1/18/1995	12	zidovudine
10/18/1995	8/2/1996	9	didanosine, zidovudine
8/13/1996	10/16/1996	2	stavudine
10/16/1996	10/15/1997	12	lamivudine, stavudine
10/15/1997	9/28/1998	11	indinavir, lamivudine, stavudine
9/28/1998	7/27/1999	10	lamivudine, nelfinavir, stavudine
7/27/1999	2/22/2000	7	amprenavir, didanosine, nevirapine, stavudine
2/22/2000	11/7/2002	32	amprenavir, didanosine, nevirapine, ritonavir
11/7/2002	6/28/2005	32	lopinavir/ritonavir, tenofovir, nevirapine
6/28/2005	1/14/2016	128	lopinavir/ritonavir, tenofovir
1/14/2016	9/20/2018	32	darunavir, ritonavir
9/20/2018	…	2	dolutegravir, etravirine

Figures Legends

Figure 1. Ultra widefield retinal photographies of the right (A) and left (B) eye show extensive areas of macular atrophy and normal optic nerve, retinal vessels, vitreous and retinal mid- and extreme-periphery.

Figure 2. Multimodal imaging of the right (A, C, E, G) and left (B, D, F, H) eye of the patient.

A, B. Infrared reflectance imaging (IR) demonstrating well demarcated hyperreflective macular atrophy associated with multiple hyperreflective dots.

C, D. Fundus autofluorescence (FAF) showing symmetric hypoautofluorescent extensive areas of RPE atrophy surrounded by a circumferential ring of speckled hyperautofluorescence pattern reaching the temporal arcades.

E, F. On FA, a window defect, corresponding to outer retinal and RPE atrophy surrounded by a heterogeneous hyperfluorescent speckled pattern.

G, H. Indocyanine green angiography showing macular hypofluorescent atrophic areas, with visualization of large choroidal vessels.

Figure 3. Spectral domain Optical coherence tomography (SD-OCT) of the right (A, C,) and left (B, D) eyes of the patient.

SD-OCT revealing complete RPE and outer retinal atrophy (cRORA) accompanied by ORT. Note the foveal sparing on the left eye with a persistent ellipsoide zone (white star).

C, D. Enhanced depth imaging SD-OCT coupled with IR allowed the colocalization of the hyperreflective dots in IR with choroidal angular hyporeflective cavities, suggestive for choroidal caverns (white arrows).

Figure 4. Optical coherence tomography angiography (OCTA) of the right (A, C, E) and left (B, D, F) eye of the patient.

A, B. Widefield swept-source optical coherence tomography angiography (SS-OCTA) revealed a large area of choriocapillaris alterations on both eyes.

C. 6x6 mm SS-OCTA showed a well demarcated area of choriocapillaris alteration, revealed by the lack of decorrelation signal (pink dotted line), allowing visualization of large choroidal vessels. D. Note the foveal sparing, with preserved choriocapillaris, on the left eye (green line) and the lack of retinal midperiphery alteration.

E, F. Corresponding B-scan showing automatic choriocapillaris segmentation.

Figure 5. Visual fields of the left (A, C, E) and right (B, D, F) eye of the patient.

A, B. Goldman visual field.

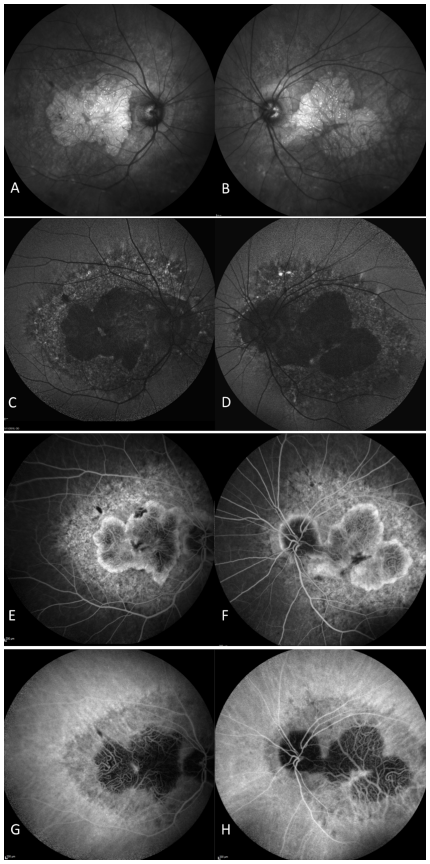
C, D. 24-2 Humphrey visual field. E, F. 10-2 Humphrey visual field.

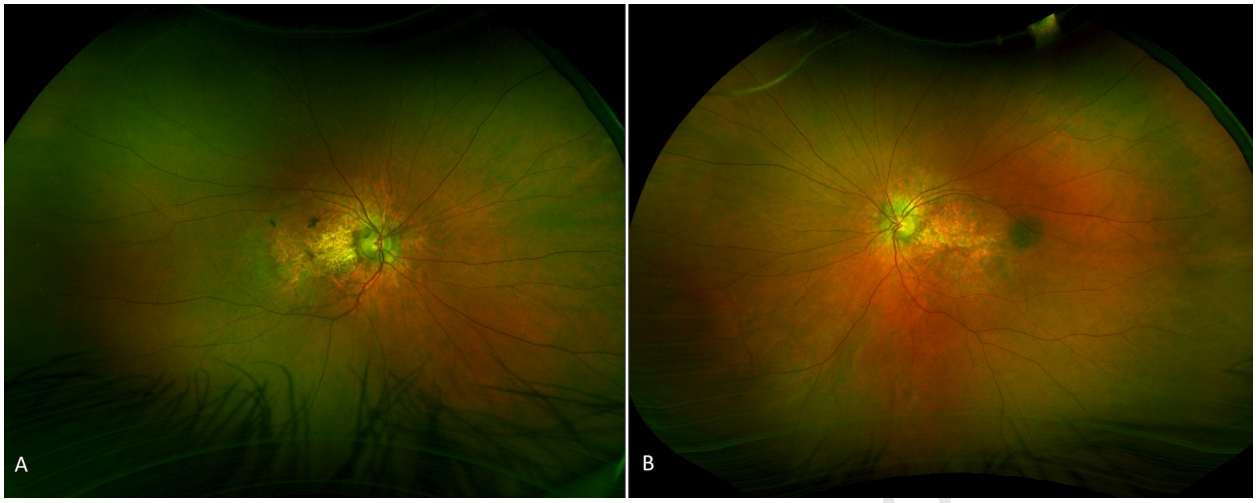
Visual fields showed a bilateral central scotoma with a preserved fixation point on the left eye.

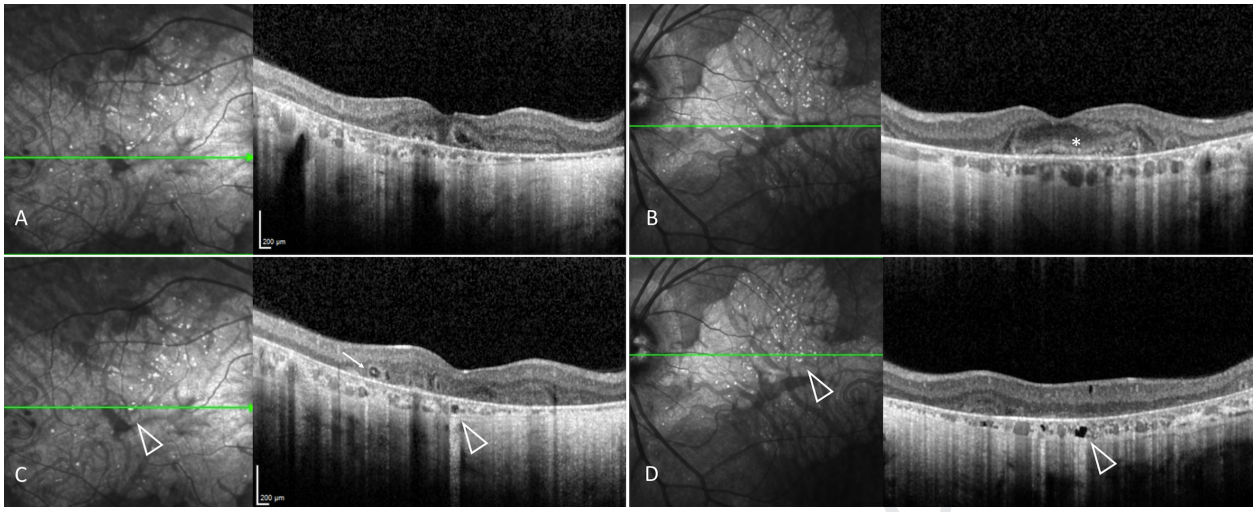
Supplementary material

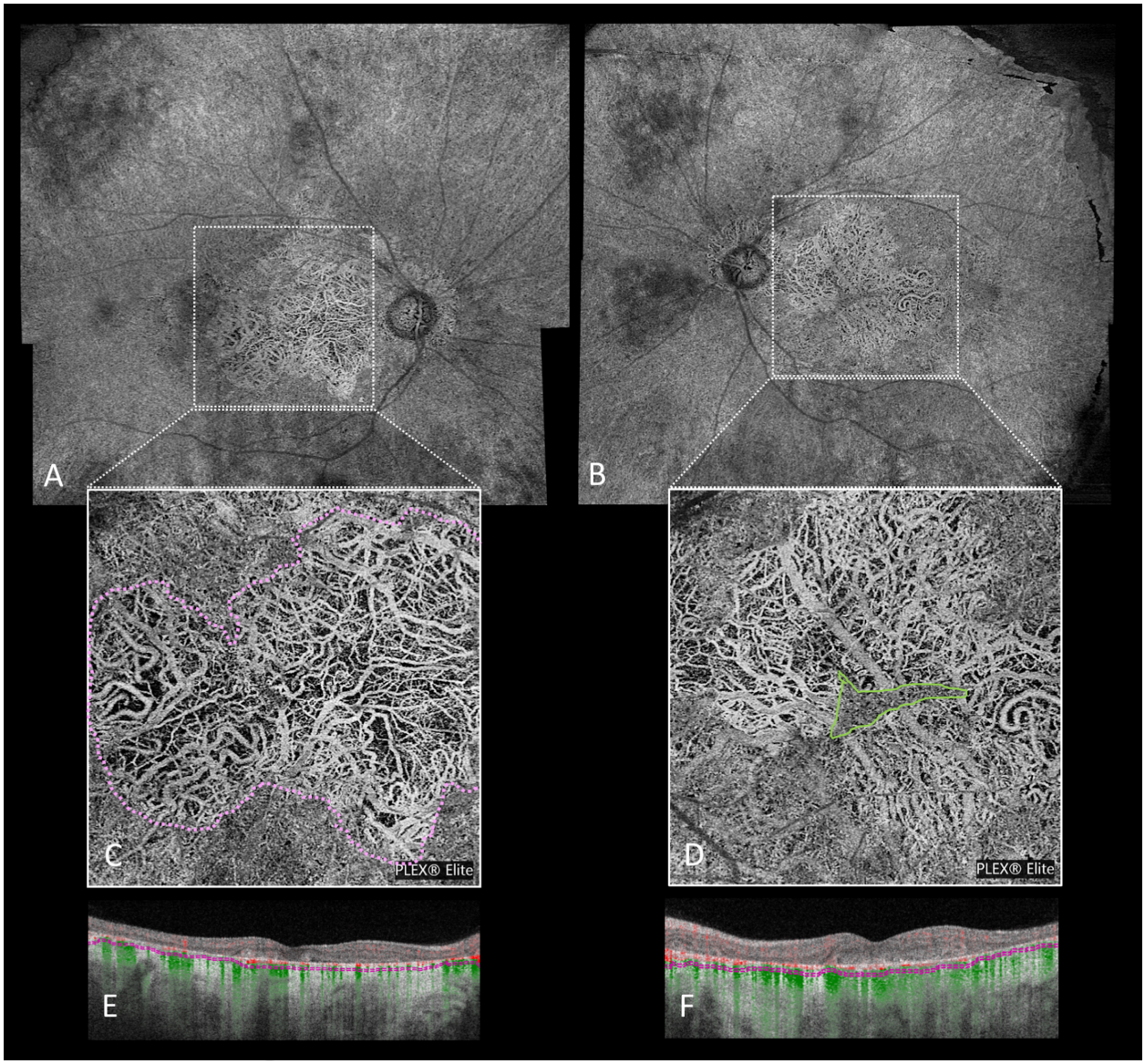
Electrophysiology testing

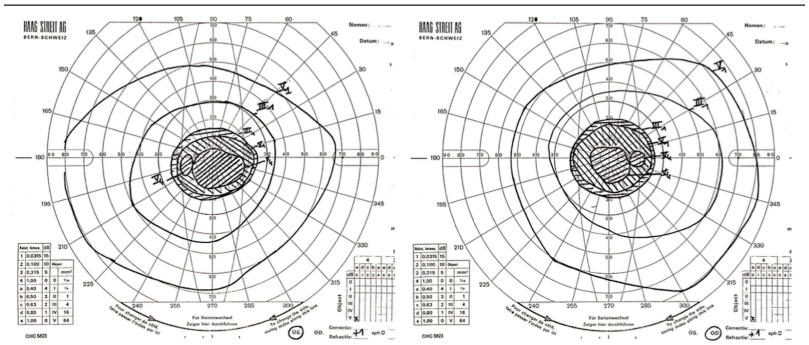
A. Full field electroretinogram demonstrating a moderated cone-rod dysfunction and increased flicker delay. B (right eye) and C (left eye) multifocal electroretinogram.



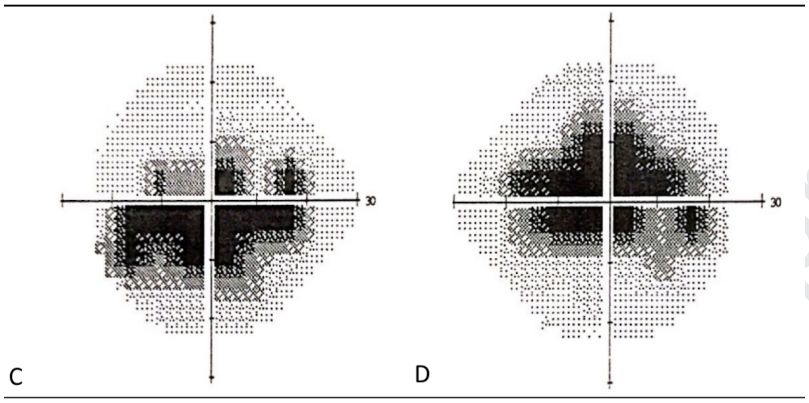




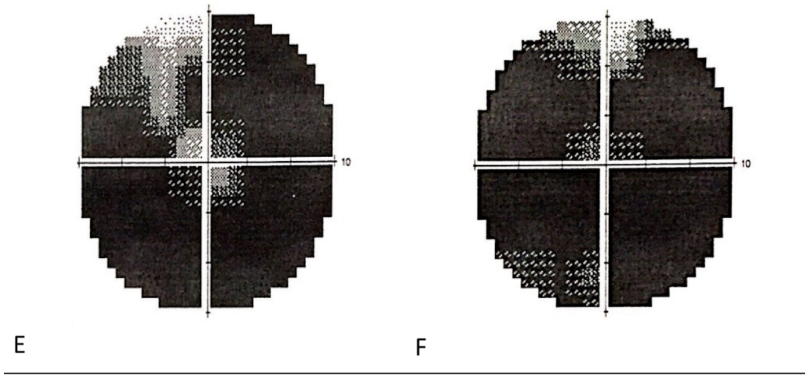

A
B
C
PLEX® Elite
D
PLEX® Elite
E
F


HAAG STREIT AG
BERN-SCHWEIZ
HAAG STREIT AG
BERN-SCHWEIZ

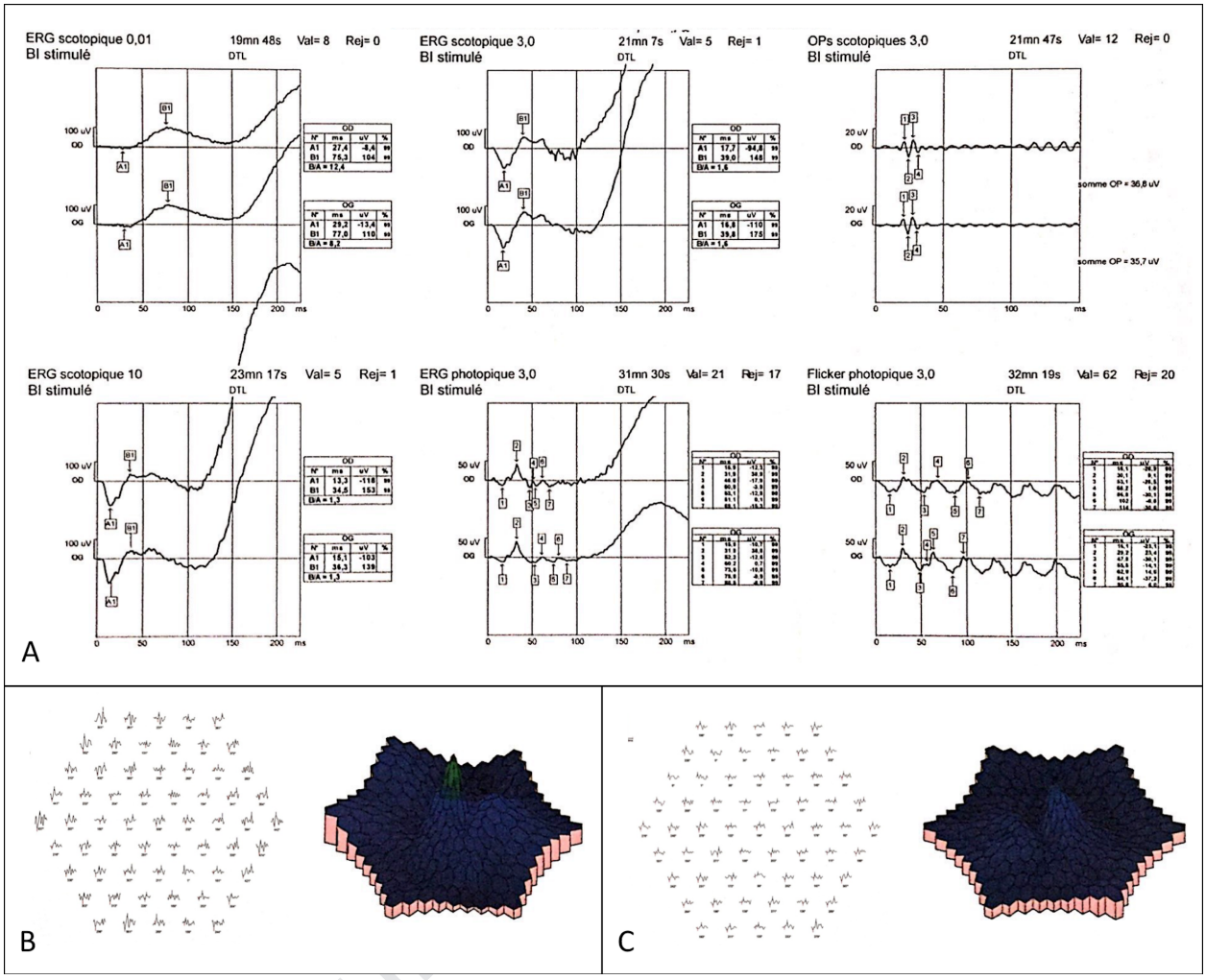
A B


30
30

C D


10
10

E F


ERG scotopique 0,01
BI stimulé
19mn 48s Val= 8 Rej= 0
DTL
ERG scotopique 3,0
BI stimulé
21mn 7s Val= 5 Rej= 1
DTL
OPs scotopiques 3,0
BI stimulé
21mn 47s Val= 12 Rej= 0
DTL
somme OP = 36,8 uV
somme OP = 35,7 uV
ERG scotopique 10
BI stimulé
23mn 17s Val= 5 Rej= 1
DTL
ERG photopique 3,0
BI stimulé
31mn 30s Val= 21 Rej= 17
DTL
Flicker photopique 3,0
BI stimulé
32mn 19s Val= 62 Rej= 20
DTL
A
B
C